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Predictive factors for the recurrence of anti-aminoacyl-tRNA synthetase antibody-associated interstitial lung disease

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ABSTRACT

Background: Anti-synthetase syndrome (ASS) is characterized by the presence of anti-aminoacyl-tRNA synthetase antibody and ASS-associated interstitial lung disease (ILD) often recurs. The effectiveness of remission induction therapy with corticosteroids and calcineurin inhibitor (CNI) and the predictive factors for ASS-ILD recurrence were examined.

Methods: We retrospectively identified consecutive patients with ASS-ILD treated with corticosteroids and CNI during 2006–2017 and evaluated the predictive factors for recurrence using logistic regression analysis.

Results: Of the 57 patients included in this study, 54 (94.7%) exhibited improved response to remission induction therapy. There were 32 recurrence patients during maintenance therapy. The median period until recurrence was 27 months. There were no significant differences in the baseline characteristics between the recurrence and nonrecurrence groups. In the recurrence group, respiratory function and St. George's Respiratory Questionnaire score deteriorated over the clinical course. The Krebs von den Lungen-6 (KL-6) level changed with disease behavior. The multivariate analysis revealed that KL-6 increase rate from remission (odds ratio: 3.21, 95% CI: 1.17–8.86, $p = 0.02$) and CNI discontinuation (odds ratio: 8.09, 95% CI: 1.39–47.09, $p = 0.02$) were independent predictive factors for recurrence. The receiver operating characteristics analysis revealed that the optimal cut-off point of KL-6 increase rate was 2.0. The positive predictive values of the KL-6

Abbreviations: ARS, aminoacyl-tRNA synthetase; ASS, anti-synthetase syndrome; CI, confidence interval; CNI, calcineurin inhibitor; CS, corticosteroid; CTD, connective tissue disease; DL_{CO}, diffusing capacity of the lung for carbon monoxide; DM, dermatomyositis; FVC, forced vital capacity; ILD, interstitial lung disease; IP, interstitial pneumonia; IQR, interquartile range; KL-6, Krebs von den Lungen-6; mPSL, methylprednisolone; PM, polymyositis; PSL, prednisolone; ROC, receiver operating characteristic; SGRQ, St. George's Respiratory Questionnaire.

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increase rate from remission of >2.0 and CNI discontinuation were 90.0 and 88.9%, respectively. The CNI treatment duration and recurrence were not related.
Conclusions: Recurrence influenced long-term deterioration. KL-6 was a serum biomarker for disease behavior and recurrence prediction. The results suggest the importance of CNI continuation.

1. Introduction

The autoantibodies against aminoacyl-tRNA synthetases (ARSs) are myositis-specific autoantibodies, which are frequently associated with interstitial lung disease (ILD) [1–3]. These autoantibodies are also detected in 6.6% cases of idiopathic interstitial pneumonia (IIP). Additionally, antisynthetase syndrome (ASS) is characterized by the presence of anti-ARS antibody [2]. Among the IIPs, the ASS-associated ILD (ASS-ILD) is an early onset disease and is highly prevalent among women [2]. The most frequent radiographic pattern in ASS-ILD is reported to be a nonspecific interstitial pneumonia pattern and ASS-ILD has a good long-term outcome [4–6]. Recently, an enzyme-linked immunosorbent assay system has been established to detect anti-ARS antibodies. The efficiency of this system is reported to be similar to that of RNA immunoprecipitation [7].

Pharmacological therapies using corticosteroids (CS) and calcineurin inhibitor (CNI) are reported to be effective for ASS-ILD [8–12]. Previous studies have also reported that the response to remission induction therapy was good with improvement rates of 64–77% [4,8]. Despite the favorable response to induction therapies, about one-third of patients with ASS-ILD were reported to exhibit long-term deterioration. However, it is difficult to predict the disease recurrence based on patient characteristics at diagnosis [4,8]. Moreover, one study reported that more than one-third of ASS-ILD cases progressed to pulmonary fibrosis [13]. Some patients with ASS-ILD exhibit disease recurrence, which is reported to cause long-term disease progression or pulmonary fibrosis [1,12].

CNI is reported to decrease the rate of recurrence [11,12]. However, the relation between CNI discontinuation and disease recurrence has not been reported. Furthermore, the impact of recurrence on long-term deterioration and the risk factors for recurrence are unknown.

The aim of this study was to evaluate the effectiveness of remission induction therapy with CS and CNI in patients with ASS-ILD. Additionally, this study aimed to determine the rate of recurrence, impact of recurrence rate on clinical course, and predictive factors for recurrence in patients with ASS-ILD.

2. Patients and methods

2.1. Study subjects

This investigation was conducted at Toseia single hospital and was approved by its institutional review board (IRB No.712, September 18, 2018). Patient approval or informed consent was waived because the study involved a retrospective review of patient records.

We evaluated consecutive patients who were newly diagnosed with ILD between December 2006 and August 2017. We retrospectively reviewed the patients diagnosed with ASS-ILD and initially treated with a combination of CS and CNI. The exclusion criteria were as follows: complications from connective tissue diseases (CTDs) other than polymyositis (PM) or dermatomyositis (DM); prior CNI treatment for more than one year at another hospital; treatment with immunosuppressants other than CS and CNI; concurrent malignancy; other severe complications. The observation period was calculated from the date of initial treatment to the date of the last visit or death. The data were collected until August 2018.

2.2. Clinical evaluation

The anti-ARS antibody was detected using an enzyme-linked immunosorbent assay kit (MESACUP™ anti-ARS test, LSI Medience Corporation, Tokyo, Japan). PM and DM were diagnosed based on the Bohan and Peter criteria for definite or probable diagnosis [14]. DM was distinguished from PM based on the presence of heliotrope rash or Gottron's lesions. The diagnosis of clinically amyopathic DM was based on the Sontheimer criteria [15]. The clinical course was classified as follows: acute (deteriorating in less than one month from the onset of respiratory symptoms or the initial visit); subacute (deteriorating in one to three months); chronic (stable or slowly progressive in more than three months) [16,17]. The high-resolution computed tomography images were obtained at end inspiration with patients in the supine position. The protocol consisted of 0.5 mm collimation sections reconstructed using a high-spatial-frequency algorithm at 10-mm intervals. ILD diagnosis was assessed and classified according to a previous study by an expert thoracic radiologist with 30 years of experience [5].

Spirometry and diffusing capacity of the lung for carbon monoxide (DL_{CO}) (both CHESTAC-55 V; Chest, Tokyo, Japan) were performed according to the American Thoracic Society/European Respiratory Society recommendations [18,19]. The 6-min walk test was conducted according to the American Thoracic Society statement [20]. The modified Medical Research Council scale was used to assess the degree of dyspnea [21]. St. George's Respiratory Questionnaire (SGRQ) was used to assess the health-related quality of life [22].

2.3. Treatment methods and response

Treatment for all patients was started with remission induction therapy, followed by maintenance therapy. All patients

were initially treated with prednisolone (PSL; 10 mg/day) and CNI as maintenance therapy. Next, we gradually reduced PSL or discontinued CNI depending on the clinical course. The initial oral dosages of tacrolimus and cyclosporine were 0.0375 and 1.5 mg/kg twice a day, respectively. The blood level of CNI was monitored and the dosage was adjusted based on the blood CNI level and toxicity. We attempted to maintain the blood trough level of tacrolimus between 5 and 10 ng/mL and that of cyclosporine between 100 and 150 ng/mL throughout the treatment duration.

The response to treatment was analyzed using the variables at 3, 6, and 12 months for the first year and every 6 months after that. The response to remission induction therapy was defined as follows: *improved* (≥10% absolute increase in percent predicted forced vital capacity (FVC)); *stable* (<10% absolute increase or <10% absolute decline in percent predicted FVC); *deteriorated* (≥10% absolute decline in percent predicted FVC). The treatment intensification over the clinical course was considered to indicate the recurrence of ASS-ILD without reference to the Krebs von den Lungen-6 (KL-6) level. The treatment intensification was defined as one of the following: (1) retreatment with methylprednisolone (mPSL) pulse, (2) increase in the PSL dosage by more than twice, (3) retreatment with or change of immunosuppressant.

2.4. Analysis of recurrence in ASS-ILD

To evaluate the predictive factors for recurrence of ASS-ILD, we analyzed the patients who exhibited improved response to induction remission therapy within 12 months. The patient characteristics at remission were ascertained at the point of their best scores within 12 months. The KL-6 increase rate from remission was calculated by dividing the maximum value of KL-6 after remission by the lowest value of KL-6 at remission.

2.5. Statistical analysis

The logistic regression analysis was used to identify the predictive factors associated with the recurrence of ASS-ILD. The variables that achieved a modest level of statistical significance ($p < 0.15$ in the univariate analysis) were assessed by multivariate analysis based on the forced entry method. The receiver operating characteristic (ROC) curve analysis was used to determine the optimal cut-off point for the prediction of recurrence, where values with maximum sensitivity and specificity were selected. The categorical variables were compared using the Fisher's exact test, while the continuous variables were compared using the Mann-Whitney *U* test. All analyses were performed using SPSS V.25 (SPSS, Chicago, Illinois, USA). The difference was considered statistically significant when the p-value was less than 0.05.

3. Results

3.1. Baseline characteristics

Of the 1581 patients screened between 2006 and 2017, 958 were tested for the anti-ARS antibody. Of these 958 patients, 103 tested positive for the anti-ARS antibody. Forty-six patients were excluded due to the following reasons: complications from CTD other than PM/DM (n = 11); prior CNI treatment for more than one year at another hospital (n = 5); combination therapy with intermittent pulse intravenous cyclophosphamide therapy (n = 1); observation or treatment without CNI (n = 26); acute exacerbation after surgical lung biopsy (n = 1); concurrent malignancy (n = 2). Thus, 57 patients with ASS-ILD treated with CS and CNI were included in this study. The baseline patient characteristics are summarized in Table 1. None of the 22 patients evaluated for anti-melanoma differentiation-associated gene 5 antibody tested positive.

3.2. Treatment course

The remission induction therapy regimens were a combination of mPSL pulse therapy (intravenous mPSL 1000 mg three days a week) for two or four weeks and CNI followed by maintenance therapy. Tacrolimus was used to treat 26 patients, while cyclosporine was used to treat 31 patients. CNI was discontinued due to adverse events in five patients during the study period. The reason for CNI discontinuation was increased serum creatinine levels (n = 5). The CNI type used to treat all these 5 patients was cyclosporine. Among the 57 patients, 54 (94.7%) and 3 patients exhibited *improved* and *stable* response to remission induction therapy during the clinical course, respectively. The median period from treatment to improvement was three months (interquartile range (IQR): 1–4). The changes in FVC, DL_{CO}, and SGRQ in the recurrence and nonrecurrence groups are shown in Supplementary Figure 1. The percentages of patients who exhibited improved response to treatment with tacrolimus and cyclosporine were 88.4% (23/26) and 96.8% (30/31), respectively. There was no significant difference in the treatment response between tacrolimus-treated and cyclosporine-treated patients ($p = 0.32$).

3.3. Recurrence of ASS-ILD

In total, 32 patients exhibited disease recurrence during the observation period. The treatment was intensified in 31 patients (96.8%) due to the deterioration of ILD with the median period of 27 months until the first recurrence. The time courses of treatment for patients with ASS-ILD in the recurrence and nonrecurrence groups are shown in Fig. 1. Of the 32 recurrence patients, 17 patients occurred after the PSL dosage was decreased, 13 patients after CNI discontinuation, and 2 patients with PSL (10 mg) and CNI treatment combination. There were no significant differences in the baseline characteristics of recurrence and nonrecurrence groups (Supplementary Table S1). No patients died at the first recurrence, whereas four patients in the recurrence group (12.5%) died due to the deterioration of ASS-ILD (median period from initial treatment to death and from recurrence to death of the four patients was 58 and 36 months, respectively).

3.4. Impact of recurrence of ASS-ILD

Of the 54 patients who exhibited improved response to remission induction therapy, 53 patients were included for

Table 1 – Baseline patient characteristics, n = 57.

Age, year	59	(52–68)
Gender, female, n	43	[75]
Smoking, n	19	[33]
BMI, kg/m^2	22.1	(20.9–23.5)
Dyspnoea rating, mMRC	1	(1–2)
SGRQ		
Symptom	43.0	33.6–61.9
Activity	53.6	36.0–66.1
Impact	30.7	18.7–40.0
Total	37.9	27.4–50.8
ILD onset, acute/subacute, n	27	[47]
Diagnosis of myositis		
PM/DM/CADM/not diagnostic, n	2/2/7/46	
CK, U/L	72	(46–232)
LDH, U/L	256	(201–352)
CRP, mg/dl	0.3	(0.1–2.2)
KL-6, U/ml	1150	(762–1780)
PaO_2 at rest, mmHg	77.5	(69.6–91.6)
PaO_2 at rest < 60 mmHg, n	4	[7]
Pulmonary function test		
FVC, %predicted	71.4	(60.8–86.8)
DL_{CO}, %predicted	57.9	(40.8–69.2)
Exercise capacity		
6MWD, m	538	(488–615)
Lowest SpO_2, %	85	(81–92)
ILD pattern on HRCT		
UIP pattern, n	1	[2]
Possible UIP pattern, n	0	[0]
Inconsistent UIP pattern, n	56	[98]
NSIP pattern, n	12	[21]
OP pattern, n	1	[2]
Organized ALI/OP with fibrosis pattern, n	37	[65]
Other/Cannot classify, n	6	[11]
BAL		
Retrieved BAL fluid, %	46	(34–57)
BAL neutrophil differential count, %	1.7	(0.4–7.2)
BAL lymphocyte differential count, %	9.2	(1.8–27.6)
BAL eosinophil differential count, %	0.8	(0.2–4.0)
Type of calcineurin inhibitor		
Tacrolimus/Cyclosporine, n	26/31	
Response to remission induction therapy		
improved/stable/deteriorated, n	54/3/0	
Observation period, month	62	(33–81)
Recurrence, n	32	[56]
Time to first recurrence, month	27	(17–35)

Values are reported as median (interquartile range) or number [%]. BMI = body mass index; mMRC = modified Medical Research Council; SGRQ = St. George's Respiratory Questionnaire; ILD = interstitial lung disease; PM = polymyositis; DM = dermatomyositis; CADM = clinically amyopathic dermatomyositis; CK = creatinine kinase; LDH = lactate dehydrogenase; CRP = C-reactive protein; KL-6 = Krebs von den Lungen-6; PaO_2 = partial pressure of arterial oxygen; FVC = forced vital capacity; DL_{CO} = diffusion capacity for carbon monoxide; 6MWD = 6-min walk distance; SpO_2 = oxygen saturation on pulse oximetry; HRCT = high-resolution computed tomography; UIP = usual interstitial pneumonia; NSIP = nonspecific interstitial pneumonia; OP = organizing pneumonia; ALI = acute lung injury; BAL = bronchoalveolar lavage.

evaluating the impact of recurrence on long-term outcomes and the predictive factors for recurrence of ASS-ILD. Only one patient was excluded as that patient exhibited stable response to remission induction therapy at 12 months (period to improvement was 25 months). The characteristics at remission of these 53 patients are shown in Supplementary Table S2. Of the 53 patients, 30 patients (56.7%) exhibited disease recurrence during the observation period. The changes in FVC, DL_{CO}, and SGRQ scores in the recurrence and nonrecurrence groups are shown in Fig. 2. Compared to the nonrecurrence group, the FVC significantly declined ($p = 0.02$) and DL_{CO} and SGRQ scores also tended to deteriorate ($p = 0.18$ and $p = 0.14$, respectively) during the observation period in the recurrence group.

The recurrence rate in patients treated with tacrolimus was lower than that in patients treated with cyclosporine (30.4% and 76.7%, respectively, $p = 0.002$). The median observation periods for tacrolimus-treated and cyclosporine-treated patients were 28.2 months (IQR: 20.2–39.1) and 29.5 months (IQR: 19.3–45.2), respectively ($p = 0.48$). The median dose of PSL at recurrence was not different between tacrolimus-treated and cyclosporine-treated patients (2.5 mg and 5.0 mg, respectively, $p = 0.532$). However, the rate of CNI discontinuation in tacrolimus-treated patients (13.0%) was significantly less than that in the cyclosporine-treated patients (50.0%) ($p = 0.008$). Moreover, the rate of CNI discontinuation as the cause of recurrence had no difference between tacrolimus-treated and cyclosporine-treated patients (28.6% and 43.5%, respectively, $p = 0.67$).

3.5. *Changes in KL-6 levels*

The changes in KL-6 levels are shown in Fig. 3. The KL-6 level at remission was less than 500 U/mL in 33 patients (62.2%) and less than 1000 U/mL in 48 patients (90.5%). In the recurrence group, the KL-6 level at recurrence increased from the KL-6 level during remission in all patients. The median KL-6 level at recurrence was 1045 (IQR: 637–1653) U/mL. However, the median KL-6 level at the last observation was 562 (IQR: 342–759) U/mL in the nonrecurrence group.

3.6. *Predictive analyses for recurrence of ASS-ILD*

The univariate and multivariate analyses of the risk factors for recurrence of ASS-ILD are shown in Table 2. In the multivariate analysis, the KL-6 increase rates from remission and CNI discontinuation were significantly and independently associated with an increased risk of recurrence ($p = 0.02$ and $p = 0.02$, respectively). The ROC curve for the KL-6 increase rate from remission as a recurrence risk factor was used to determine the cut-off values (Supplementary Figure 2). The area under the curve was good and the KL-6 increase rate from remission of 2.13 corresponded to the maximum joint sensitivity and specificity on the ROC curve (60.0% sensitivity and 95.7% specificity). For easy use in clinical practice, we judged a KL-6 increase rate from remission of >2.0 to be a reasonable cut-off value for predicting recurrence. The KL-6 increase rates from remission of >2.0 had 60.0% sensitivity and 91.3% specificity. The median days from KL-6 increase rates from remission of >2.0 to recurrence were 61 days (IQR: 9–158). CNI discontinuation had 53.3% sensitivity and 91.3% specificity (Supplementary Table S3). Among the 16 patients with recurrences after CNI discontinuation, there was no relation between CNI treatment duration and recurrence (Table 3).

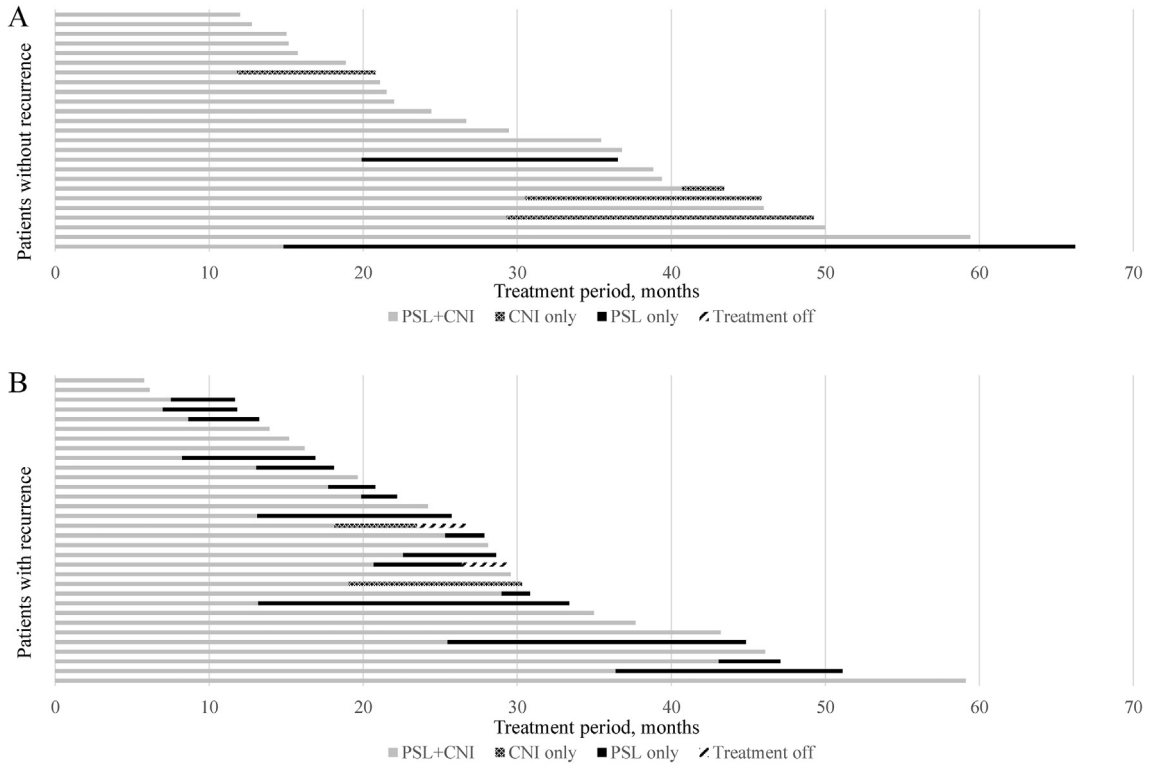

Fig. 1 – (A) Treatment period in patients with ASS-ILD not exhibiting disease recurrence. (B) Treatment period until recurrence in patients with ASS-ILD exhibiting recurrence. ASS, anti-synthetase syndrome; ILD, interstitial lung disease; PSL, prednisolone; CNI, calcineurin inhibitor.

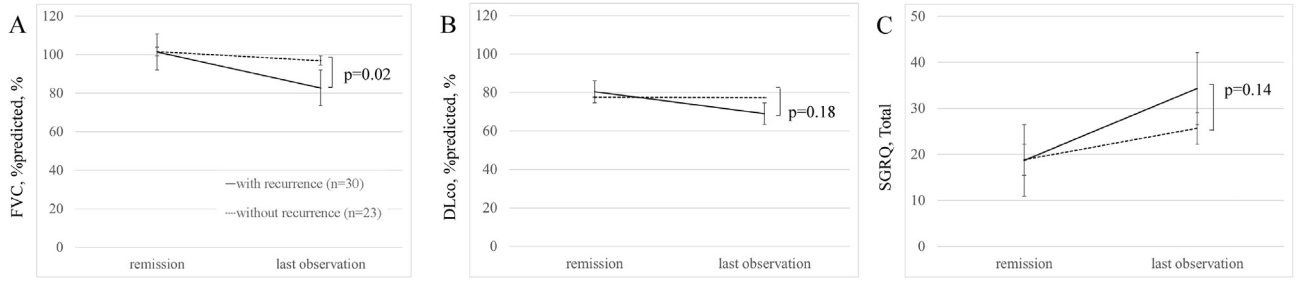

Fig. 2 – Changes in FVC (A), DL_{CO} (B), and SGRQ scores (C) ± standard error at remission and last observation. Comparison between patients with ASS-ILD in the recurrence and nonrecurrence groups. FVC, forced vital capacity; DL_{CO}, diffusing capacity of the lung for carbon monoxide; SGRQ, St. George's Respiratory Questionnaire; ASS, anti-synthetase syndrome; ILD, interstitial lung disease.

4. Discussion

We analyzed the patients with ASS-ILD treated with CS and CNI to evaluate the relation between recurrence and clinical course and to elucidate the predictive factors for recurrence. In this study, 95% of patients exhibited improved response to remission induction therapy. Of these patients, 56% exhibited disease recurrence. The disease recurrences resulted in the long-term deterioration of respiratory function and SGRQ scores. The independent risk factors for recurrence were CNI discontinuation and KL-6 increase rate from remission. These results suggest the importance of CNI and recurrence avoidance in the management of ASS-ILD.

Our treatment strategy for patients with PM/DM-ILD was a combination of CNI intravenous mPSL administration followed by low dose PSL administration (10 mg/day). The treatment strategy was well tolerated and had multidimensional efficacy against PM/DM-ILD [23,24]. In this study, the improvement rate of remission induction therapy was 95%, which was higher than that in previous studies that reported improvement rates of 64–77% in patients with ASS-ILD [4,8]. This suggested the effectiveness of initial CNI therapy [8,10–12]. However, the frequency of recurrence was 56%. In the recurrence group, the long-term deteriorations in respiratory function and SGRQ scores, which are considered to be useful tools for assessing the health-related quality of life in CTD-ILD, were higher than those in the nonrecurrence group [24–27]. Therefore, the

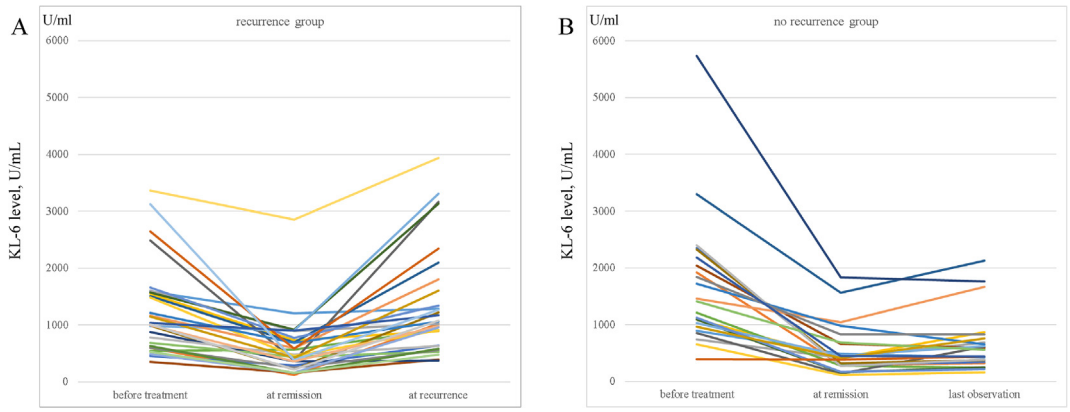

Fig. 3 – Changes in KL-6 level associated with disease behavior of ASS-ILD in the recurrence group (A) and nonrecurrence group (B). KL-6, Krebs von den Lungen-6; ASS, anti-synthetase syndrome; ILD, interstitial lung disease.

Table 2 – Univariate and multivariate analyses of the risk factors for recurrence of ARS-ILD.

	Univariate analysis					Multivariate analysis				
	OR	95% CI			P-value	OR	95% CI			P-value
ILD onset, acute/subacute, yes	1.49	0.50	–	4.43	0.48					
Organized ALI/OP with fibrosis pattern on HRCT, yes	1.29	0.42	–	3.98	0.66					
FVC at remission, %predicted	0.999	0.97	–	1.03	0.96					
DL_{CO} at remission, %predicted	1.01	0.98	–	1.04	0.58					
SGRQ at remission	0.999	0.99	–	1.04	0.97					
KL-6 at remission, $*10^2$ U/ml	1.01	0.90	–	1.14	0.83					
KL-6 increase rate from remission	3.64	1.50	–	8.81	<0.01	3.21	1.17	–	8.86	0.02
CNI discontinuation, yes	12.00	2.38	–	60.52	<0.01	8.09	1.39	–	47.09	0.02

ARS = aminoacyl-tRNA Synthetase; ILD = interstitial lung disease; OR = odds ratio; CI = confidence interval; ALI = acute lung injury; OP = organizing pneumonia; HRCT = high-resolution computed tomography; FVC = forced vital capacity; DL_{CO} = diffusion capacity for carbon monoxide; SGRQ = St. George's Respiratory Questionnaire; KL-6 = Krebs von den Lungen-6; CNI = calcineurin inhibitor.

Table 3 – Relationship between CNI continued period and recurrence (n = 18).

	CNI continued period			
	$t \leq 6$ M	6 M < $t \leq$ 12 M	12 M < $t \leq$ 24 M	24 M < t
CNI discontinuation, n	0	3	10	5
Recurrence, n	0	3 [100]	8 [80]	5 [100]
From CNI discontinuation to recurrence, month	.	4.8 (4.2–8.7)	5.7 (3.3–11.6)	4.0 (2.5–17.2)

Values are reported as median (interquartile range) or number [%]. CNI = calcineurin inhibitor.

treatment strategies for ASS-ILD must be devised to avoid disease recurrence. However, there are no studies that have reported the risk factors for the recurrence of ASS-ILD.

In this study, CNI discontinuation was significantly associated with the recurrence of ASS-ILD ($p = 0.02$). Previous studies have reported that CNI decreases the rate of recurrence [11,12]. However, the relation between CNI discontinuation and recurrence has not been reported. In this study, the recurrence rates in the CNI continued and CNI discontinued groups were 39 and 89%, respectively. The multivariate analysis revealed that the CNI discontinuation was an independent risk factor for the recurrence of ASS-ILD. Additionally, there was no relation between CNI treatment duration and recurrence. The recurrence occurred relatively early after CNI discontinuation even after CNI had been continued for a long time. These results suggested the importance of CNI in the treatment of ASS-ILD.

CNI works effectively by inhibiting the activation of T cells. The nuclear translocation of the activated T cell nuclear factor is blocked by CNI, which results in an immunosuppressive effect by inhibiting the production of interleukin-2 and other cytokines [28,29]. Although the pathogenesis of PM/DM-ILD has not been fully elucidated, the activated Th1-type pulmonary T cells are reported to play an important role in the development of CS-resistant PM/DM-ILD [30]. This indicates that T cells may be an essential therapeutic target and that CNI may be an important therapeutic agent.

Furthermore, tacrolimus is reported to suppress the synthesis of collagen and the expression of tumor growth factor-β type I receptor in the lung fibroblasts [31]. A recent study reported that FK506 (tacrolimus)-binding protein 10 expression was upregulated in bleomycin-induced lung fibrosis, while the loss of FK506-binding protein 10 expression suppressed the collagen secretion. This suggested that the inhibition of

FK506-binding protein 10 may contribute to the antifibrotic effects of tacrolimus [32].

In this study, the change in the KL-6 level was an independent predictive factor for the recurrence of ASS-ILD. KL-6 is a high-molecular-weight glycoprotein that is classified as MUC1 mucin, which was initially reported to be a serum biomarker for disease activity of interstitial pneumonitis [33,34]. Recently, KL-6 was reported to be a useful serum biomarker in CTD-ILD [35–37]. However, the role of KL-6 in predicting recurrence of ASS-ILD has not been elucidated. Our study demonstrated that KL-6 changed with the disease behavior of ASS-ILD and that the KL-6 increase rate from remission is an important predictor of recurrence. These results suggest that monitoring KL-6 can predict the early phase of recurrence and aid in modifying the treatment to avoid progressive recurrence.

This study has several limitations. This is a retrospective study with a small sample size from a single institution. However, the results are reliable as there is a very small amount of missing data. Additionally, we have not determined the standards for decreasing the PSL dosage or the protocols related to the discontinuation of CS and CNI. However, the treatment strategy is decided through consultation at a conference and the treatment content is relatively uniform. Therefore, we believe our treatment is consistent. Furthermore, we detected anti-ARS antibody using MESACUP™ enzyme-linked immunosorbent assay, which cannot detect the anti-OJ, anti-Zo, and anti-Ha antibodies. Finally, azathioprine, methotrexate, or mycophenolate mofetil are globally used as first-line glucocorticoid-sparing agents. However, these drugs are not approved for treating ASS-ILD in Japan and CNI has been selected as one of the standard therapeutic agents. Further comparative studies involving a larger cohort of patients are needed to confirm our results.

5. Conclusions

Disease recurrence influenced the long-term deterioration of ASS-ILD. The KL-6 level is a useful serum biomarker for disease behavior and prediction of recurrence in ASS-ILD. As CNI discontinuation was a risk factor for recurrence, continuation of CNI may be necessary to maintain remission. Further prospective and randomized controlled studies are needed to establish treatment strategies for ASS-ILD.

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Declaration of competing interest

Dr. Kondoh receives advisory board fees and personal fees from Asahi Kasei Pharma Corp., and personal fees from Boehringer Ingelheim Co., Ltd., Eisai Inc., Kyorin Pharmaceutical Co., Ltd., Novartis Pharma K.K., Shionogi & Co., Ltd., and Teijin Pharma LTD outside the presentation work. The other authors have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resinv.2019.10.004.

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